EXHIBIT 68

RISK MINIMIZATION ACTION PLAN

For

OPANA® ER (Oxymorphone Hydrochloride) Extended-Release Tablets

June 2007

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CONFIDENTIALITY STATEMENT

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AAFP	American Academy of Family Physicians
AAPCC	American Association of Poison Control Centers
AAPM	American Academy of Pain Medicine
ACCME	Accreditation Council for Continuing Medical Education
ACP	American College of Physicians
ACPE	Accredited Pharmacy Education
APS	American Pain Society
ASI-MV	Addiction Severity Index-Multimedia Version
CE	Continuing Education
CME	Continuing Medical Education
D4R	*Drugs4Real*
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Agency
DOJ	Department of Justice
ER	Extended release
ESRB	Endo Safety Review Board
FDA	Food and Drug Administration
FOI	Freedom of Information
HHS	Health and Human Services
HHS-OIG	Department of Health and Human Services-Office of Inspector General
IR	Immediate release
IVR	Interactive Voice Recognition
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
MCO	Managed Care Organizations

Abbreviation	Definition
MSB	*MyStudentBody*
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIPC	National Initiative on Pain Control
OWH	Office of Women's Health
PBM	Pharmacy Benefits Management
QISP	Quantitative Internet Surveillance Program
RADARS	Researched Abuse, Diversion and Addition Related Surveillance
RiskMAP	Risk Minimization Action Plan
SAMHSA	Substance Abuse and Mental Health Services Administration
SOAPP	Screener and Opiate Assessment for Patients With Pain
SPC	Statistical Process Control
STFM	Society of Teachers of Family Medicine
TEDS	Treatment Episode Data Set
TESS	Toxic Exposure Surveillance System
US	United States

1. BACKGROUND

Intractable chronic pain drains its victims of quality of life and the United States (US) economy of billions of dollars in healthcare costs and lost productivity. Multiple studies have confirmed the usefulness of opioids in the treatment of chronic pain and cite the relatively low incidence of abuse and addiction among most patients who receive opioid analgesics. The literature further suggests that the potential for increased functioning and improved quality of life significantly outweigh the risk of abuse (American Academy of Pain Medicine, 1997). Professional organizations, such as the American Pain Society (APS) and American Academy of Pain Management, recognize the benefits of adequate pain management and the pivotal palliative role for opioids in the treatment of chronic non-cancer pain, as well as moderate-to-severe acute pain (American Academy of Pain Medicine, 1997).

Unfortunately, prescription opioid analgesics, like all medications, are associated with a number of risks. Chief among these are the risks of abuse, misuse, and addiction. According to the 2004 National Household Survey on Drug Use and Health, people who had used pain relievers' non-medically at least once during their lifetime increased 7% from 2002 to 2004, for a total of 31.8 million Americans (Gfroerer, 2003). The reported rise of prescription drug abuse is corroborated by data on the consequences of such use. According to Substance Abuse and Mental Health Services Administration's (SAMHSA's) Drug Abuse Warning Network (DAWN), emergency department contacts for non-medical use of substances for psychic effects, overdose, dependence, or suicide attempts increased from 69,011 in 1999 to 119,185 in 2002 for narcotic analgesics. The Treatment Episode Data Set (TEDS), also administered by SAMHSA, collects data on admissions to federally funded drug and alcohol addiction treatment programs noted that between 1999 and 2003, treatment admissions for opiate drug addiction treatment (exclusive of heroin) increased from 1,382 admissions in 1999 to 9,171 in 2003.

Importantly, nearly half of the prescription drug abuse has been observed in youth and young adults (aged 12 to 25) (Gfroerer, 2003). Use of these drugs by young people has dramatically increased for all categories of pharmaceuticals, most prominently pain relievers (nearly 2 million in 2000), followed by tranquilizers (nearly 1 million) (Gfroerer, 2003).

The first step in addressing any public health problem is appropriate surveillance; yet, existing surveillance systems for prescription opioid abuse, including those cited above, have been widely acknowledged as inadequate (Arfken, 2003; GAO, 2003). At this point in time, real-time product-specific surveillance does not exist. Existing databases either provide data several years after the fact (e.g. National Survey of Drug Use and Health), or do not discriminate with any known degree of accuracy between abuse rates of specific products (e.g. key informant

networks). Discussions about risk management mean little without up-to-date product specific information; Endo has recognized and begun to address this need.

While addiction in patients prescribed opioids for pain appears to be uncommon, there is little doubt that it occurs (Hays, 2004). Although lack of training of physicians and other healthcare providers in pain treatment and substance abuse management is an enormous problem, it is also apparent that even in the hands of well trained physicians, some patients develop abuse problems that are difficult to detect and manage (Katz, 2003). There is a clear cut need to develop not only widely available training programs for healthcare providers, but new tools to better assess risk of abuse in patients with chronic pain (Butler, 2004) (see Section 3.2.3).

An additional problem receiving increasing attention is the danger associated with co-ingestion of alcohol with opioid analgesics. Proactive education and dissemination of clinical practice tools are needed to help patients and their clinicians minimize the common side effects of opioids, including minimizing the consequences of alcohol co-ingestion.

As a pharmaceutical company focused on the improvement of pain management, Endo Pharmaceuticals Inc. (Endo) feels a strong sense of responsibility to improve the care of pain for patients while at the same time safeguarding against potential misuse of its products. Improving pain management includes the development of novel effective analgesics and also ensuring the proper and appropriate use of its medication. Thus, Endo has developed and is constantly striving to improve a comprehensive Risk Minimization Action Plan (RiskMAP) for OPANA® ER, which aims to promote the safe and responsible use of the product while concurrently minimizing abuse, misuse, diversion, and other adverse events through appropriate drug labeling, tight controls on distribution, proactive pharmacovigilance, extensive education of healthcare professionals and sales personnel, and funding of clinically meaningful research.

The most recent extensive public discussion of opioid risk management programs took place in September, 2003, at the meeting of the Anesthetic and Life Support Drugs Advisory Committee of the US Food and Drug Administration (FDA). The key messages of that meeting with regard to risk management were:

- The product label should include recommendations for routine assessment of addiction risk and outcomes, although tools to assist physicians in this task were lacking
- Improved monitoring and surveillance of patients on opioid therapy was needed
- Education on opioid prescribing and abuse risks must be made widely available to clinicians

- The major limitations of existing surveillance systems were:
  - No information on pathways to prescription opioid abuse
  - No information on the risk of addiction among patients with chronic pain
- Pharmaceutical companies on their own should not determine when a pattern of opioid prescribing or patient behavior should be viewed as inappropriate
- In addition, the committee felt that the following research efforts were necessary, however not by pharmaceutical companies:
  - Criteria for diagnosis of addiction in the pain management setting
  - Rates of addiction in patients on opioid therapy
  - Risk factors for prescription opioid abuse
  - Effectiveness of interventions for reducing prescription opioid abuse among pain patients
  - Characteristics of prescription opioid abusers
  - Sources of abused prescription opioids

Endo has taken the output of this advisory committee very seriously. The comprehensive RiskMAP described below addresses a number of points raised by the advisory committee, as summarized above. It is our hope that the vision articulated by the advisory committee for the ideal opioid risk management program will be brought significantly closer to reality through our efforts as described below.

In summary, Endo recognizes that access to opioid analgesics is critical for the millions of people suffering from chronic pain, but that the risks of prescription opioids, including addiction and diversion, must also be addressed. To that end, the following RiskMAP has been developed and was implemented at the time OPANA ER was marketed. It is Endo's belief that this comprehensive RiskMAP will help protect the public and aid in minimizing the abuse, misuse, and diversion of its OPANA products.

2. GOALS AND OBJECTIVES

The goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to OPANA ER.

- Aberrant behavior such as drug abuse, misuse, and addiction
  - Among patients

- In the community, particularly among young adults

- Unintentional drug overdose
- Accidental exposure
- Diversion from distribution/manufacturing facilities
- Improper patient selection
- Fraudulent prescription activity
- Inadequate patient education

A substantial initiative is to facilitate all of the above goals with improved approaches to surveillance.

3. STRATEGY AND TOOLS

The Strategy and Tools were developed to minimize the potential risks that may be associated with OPANA ER and thus Endo's RiskMAP is designed to protect the public and help minimize abuse, misuse, and diversion.

3.1 Product Labeling

Endo has worked with the Agency to develop approved product labeling that adequately instructs healthcare providers and patients in the safe and appropriate use of the product. The Package Insert contains the appropriate language needed to inform healthcare providers and patients of the risks associated with the product and the information required to help minimize the risk of abuse, misuse, and diversion.

Endo submitted a Patient Package Insert as part of the labeling for oxymorphone ER. The Patient Package Insert translates the Package Insert into terms understandable by a typical patient (approximately a sixth-grade level). The oxymorphone Patient Package Insert contains the following information.

- Most important information regarding the medication
- Accidental overdose by children
- Co-ingestion with alcohol
- Side-effects of the treatment

3.2 Education

Endo has developed and implemented, and will continue to support the development and implementation of, educational initiatives for physicians, pharmacists, nurses, and other allied healthcare professionals on the appropriate use of opioid analgesics with a particular emphasis on modified-release opioids. Educational initiatives for patients, their families, and caregivers will emphasize safe and appropriate use as well as discuss resources to contact for further assistance with questions and concerns regarding opioid medication use.

Although the sponsor funds these educational programs through unrestricted educational grants, and thus relinquishes control of content to the authors, faculty, and CE providers, the Sponsor will stress the requirement for discussion of risk management and request that the following elements be considered in the planning of all opioid-related programs.

- Careful selection of patients for whom a modified-release opioid is appropriate (type and duration of painful condition)
- Initial assessment of patient including pain assessment tools prior to initiation of therapy with a modified-release opioid
- Regular reassessment of patient once therapy is initiated
- Identification of patients at higher risk for abuse and diversion, and available management tools for this special population
  - Screening tools (e.g. SOAPP)
  - Patient-physician agreement
  - Frequency of follow-up
  - Role of drug screening to monitor compliance
- Appropriate ongoing documentation for patients prescribed a long acting opioid
- The importance of patient and family/caregiver education
- Actions for minimizing the potential risk for abuse and misuse
- Action for minimizing the potential risk of accidental exposure
- Differentiation among states of physical dependence, tolerance, pseudoaddiction, and addiction
- Avoiding co-ingestion with alcohol
- Tapering off opioid therapy in patients for whom opioids have proven unhelpful

Professional and patient education initiatives with risk management components include but are not limited to those described in the following sections.

3.2.1 Professional Education Initiatives

3.2.1.1 National Initiative on Pain Control (NIPC)

The "National Initiative on Pain Control" (NIPC) is a CME-accredited educational program solely supported by Endo, which was established to advance clinicians' understanding of pain assessment/treatment, and to improve outcomes for patients with chronic pain. These programs are based upon a common slide kit developed by the NIPC Education Council, an educational advisory group of thought leaders in the area of pain management and opioid pharmacotherapy for the treatment of pain who are solely responsible for curriculum content and development. Once the curriculum has been developed, a core group of faculty is trained by the Education Council and the CME sponsor to deliver the programs. The faculty consists of physicians, nurses and pharmacists with an established expertise in the diagnosis and treatment of chronic pain, including the appropriate use of opioid analgesics.

The intended audience for the NIPC initiatives includes 60,000 internists, family physicians, osteopathic medicine specialists, general neurologists, physical medicine and rehabilitation specialists, and other clinicians who manage patients with chronic pain.

To date, the following two live-CME modules, specifically addressing the responsible prescribing of opioid analgesics, have been developed for the NIPC curriculum:

- "Opioid Analgesia: Practical Treatment of the Patient with Chronic Pain"
- "Advances in Opioid Analgesia: Maximizing Benefit; Minimizing Harm"

These modules have also been integrated into a half-day symposium format entitled:

- "Optimizing Patient Outcomes in Pain Management: New Strategies for Today's Clinical Practice"

In addition, an audioconference module has been developed to extend the reach of the opioid education initiatives and for physicians unable to attend.

- "Opioid Analgesia: Enhancing Pain Management and Patient Outcomes"

This module may also be utilized in rural or difficult to access geographies, or can be tailored by the CME provider for use in targeted interventional areas.

The NIPC programs have been supported through an unrestricted educational grant from Endo since the initiative's inception in 2001; Endo is the sole grantor supporting the NIPC and plans to continue grant support for NIPC indefinitely. For 2005/2006, the opioid educational initiatives were offered via various educational media such as:

- CME-accredited Dinner Dialogue™ Programs
- CME-accredited Audioconferences
- CME-accredited half-day symposia
- CME-accredited newsletters
- CME-accredited Webcasts

During 2005/2006, these programs were implemented to educate clinicians nationwide on proper patient assessment, selection, and follow-up with regards to the use of modified-release opioids for the treatment of chronic pain. In addition, Endo has suggested to the CE provider that programs appropriate for pharmacists be added to the curriculum.

The following materials that have been developed to date for the NIPC opioid analgesic modules include:

NIPC Core Curriculum/Faculty Guide

The NIPC core curriculum/faculty guide consists of all core curriculum slides, speaker notes, and references utilized by the NIPC visiting faculty. This guide describes the learning objectives, reviews the ACCME requirements, and includes the curriculum materials and references.

NIPC Participant Guide

This guide is provided to every participant in the live CME-accredited lectures and symposia. The purpose is to reiterate the CME learning objectives, to provide hard copies of the core curriculum slides, and to provide space for participants to record notes on the faculty presentations. Each participant guide also contains a copy of the CD-ROM resource kit, which the clinician can utilize to improve patient management. The kit includes an innovative patient care algorithm designed to simplify opioid prescribing for the primary care physician. The algorithm emphasizes previously neglected areas of opioid management including management

of side effects, assessment of abuse, and exit strategies from opioid therapy when appropriate. This program will aid clinicians with appropriate patient selection and promote safe opioid use.

NIPC Audioconference Guide

This guide is provided to all registrants in the interactive audio conferences. The audioconference guide provides a means for the participants to view the core curriculum slides at their desks, while participating in the interactive audioconference. Each audioconference guide also contains a copy of the CD-ROM clinician resource kit.

NIPC Pain Management Today Newsletter

The NIPC ***Pain Management Today*** newsletter is a 12 page CME-accredited publication distributed bi-annually to 60,000 physicians who manage chronic pain patients. The publication is intended as a resource, which provides timely articles of clinical importance, patient assessment/management resources, case studies, and a clinical Q&A forum on chronic pain.

3.2.1.2 The Office of Women's Health of the US Department of Health & Human Services: "Breakthroughs & Challenges in the Management of Common Chronic Pain Disorders" Initiative

National CME-accredited initiative presented by the Office of Women's Health (OWH) Department of Health and Human Services (HHS), and chaired by Richard Payne, MD and Christine Miaskowski, RN, PhD, two nationally-recognized experts in the field of pain management and opioid analgesics.

The initiative consisted of a 3-day faculty meeting to discuss the most recent advances in managing chronic pain, followed by the development of a slide curriculum and a series of enduring materials, which are being disseminated under the auspices of OWH/HHS and various national professional societies.

A substantial portion of the curriculum focuses on the responsible use of opioid analgesics for chronic pain disorders, including clinical and risk management considerations. The target audience for the educational materials is family physicians, internists, neurologists, anesthesiologists, physical medicine and rehabilitation, and other clinicians who treat chronic pain. The first in a series of enduring materials from this meeting was published and distributed in 3Q 2004; additional enduring materials were distributed in 2005 and updated in 2006.

3.2.1.3 Satellite Symposia & Initiatives in Collaboration with Professional Societies

Endo recognizes the importance of peer-to-peer education via national congresses and professional societies as a means of advancing clinicians' knowledge about the responsible prescribing of opioid analgesics. To this end, Endo has and will continue to support satellite symposia and educational programs in conjunction with professional congresses or societies such as:

- American College of Physicians (ACP)
- American Academy of Family Physicians (AAFP)
- Society of Teachers of Family Medicine (STFM)
- American Pain Society (APS)
- American Academy of Pain Medicine (AAPM)
- American Academy of Pain Management
- American Society of Addiction Medicine
- Annual Conference on Pain & Chemical Dependency
- PriMed Primary Care Regional Education Conferences
- Multi-National Association for Supportive Care in Cancer
- American Society of Pain Management Nurses
- Oncology Nursing Society
- American Society of Health System Pharmacists
- Academy of Managed Care Pharmacy
- Other regional pain education symposia

These symposia and initiatives are scheduled in conjunction with the above-listed Congresses, and/or professional society meetings. Again, these satellite symposia are funded through unrestricted educational grants provided to the professional societies or CE providers. The Sponsor will continue to make the organizers aware of the need for balance on the issues of risk management.

3.2.1.4 Physician-in-Training and Primary Care Initiatives

Endo recognizes the need to educate physicians-in-training and primary care physicians on appropriate pain assessment, responsible prescribing of opioid analgesics and appropriate patient follow-up which optimizes pain relief while minimizing the potential for adverse events, including medication misuse.

The following programs, supported through unrestricted educational grants from Endo, focus on these key groups of clinicians:

- American Pain Society (APS) Residents Course – an annual 2-day course taught to approximately 100 residents from family medicine, internal medicine, neurology, anesthesiology, physical medicine/rehab, and emergency medicine. Several hours of the course focus on opioid-related issues including: appropriate patient selection, practical prescribing considerations, side effects, patient follow-up and documentation, and addiction/dependence/abuse/diversion issues. Endo initiated this course in 2001 and has been the sole supporter for the course every year since via an unrestricted educational grant to Northshore/Long Island Jewish Health System. This course takes place annually prior to the APS Meeting.
- American Academy of Family Physicians (AAFP) – a 3 hour AAFP evidence-based CME video and educational monograph entitled "Managing Pain: Dispelling the Myths." This monograph, which has been distributed to all AAFP members, examines the appropriate assessment and management of pain, including: responsible use of opioid analgesics, discussion of controlled substances, abuse, addiction, pseudoaddiction, physical dependence, and tolerance.
- Society of Teachers of Family Medicine (STFM) – for the past 3 years Endo has supported a full day pre-course at this annual meeting for family medicine faculty and residency program directors. The course, developed and presented by the STFM's Pain Management Interest Group, focuses on the essential principles and practice of pain assessment and management. A substantial amount of didactic and interactive discussion time is focused on the appropriate prescribing of opioid analgesics, clinical considerations, and abuse/misuse/addiction/diversion issues. This course occurred in 2004 and 2005; a similar initiative is planned for 2006.
- California Primary Care Course – 12 hour CME-accredited course developed to educate primary care physicians in California on the principles/practice of pain management, including several hours related to appropriate prescribing of opioid analgesics, appropriate patient selection, proper education and follow-up, and addiction/abuse/diversion issues. Endo is the sole grantor for this Course which was offered in 2003-2005; a similar program is planned for 2006.

- American College of Physicians (ACP) – 3-hour workshop on Pain Management at the national ACP meeting. A substantial portion of this workshop for internists focuses on the appropriate use of opioid analgesics, patient selection and follow-up and addiction/abuse/diversion issues. This Workshop took place during 2004; during 2005, an enduring material was published/distributed to all ACP members. Additional pain management initiatives with the ACP are planned for 2006.
- PriMed Conferences – symposia at these annual meetings of primary care physicians have occurred for the past two years and are planned for 2006. Significant time is devoted to appropriate prescribing of opioid analgesics, as well as side effects and the potential for misuse/diversion. Following the conference, CME-accredited enduring materials are distributed to primary care physicians.

Endo plans to continue the above initiatives, or similar educational initiatives post-approval.

3.2.1.5 *www.Painedu.org* Website and Manual

This initiative consists of a website and pocket manual created by Inflexxion, a science-based, interactive healthcare technology company. Inflexxion develops web-based programs for clinicians and consumers. It also develops and tests clinical measurement scales and assessment tools. As well as providing programs and services to healthcare and substance abuse organizations around the country, Inflexxion works extensively with the pharmaceutical industry and in particular companies with pain products. *PainEdu* utilizes nationally-recognized experts within the behavioral health, oncology, pain medicine and addiction medicine fields to develop content for both the website and the pocket manual.

The site is highly interactive and makes use of case-based learning, roundtable discussions, 'ask the expert' modules, downloadable tools such as the SOAPP, an electronic download of the Clinical Companion manual and makes use of varied educational strategies. Further, *PainEdu* provides online continuing education credits to physicians, psychologists, nurses and pharmacists. The site is used actively by healthcare professionals and has nearly 6,000 registered users as of October, 2005. It has received an award for provider education excellence and was cited by the APS Newsletter as a very valuable resource.

For the past four years, Endo has supported the development, maintenance and continued enhancement of *PainEdu* through an unrestricted educational grant.

3.2.1.6 ACPE-Accredited Pharmacy Education Monographs

Endo has supported the development of ACPE-accredited monographs to educate pharmacists on the proper role of modified-release opioid analgesics for the treatment of chronic pain. These educational materials discussed the clinical/risk management considerations, and stress the importance of the relationship between the prescribing physician and the pharmacist in detection of abuse or diversion of opioid analgesics.

The monographs were distributed to all pharmacy specialties, including retail independent, retail chain, consultant pharmacists, hospital pharmacists, and HMO-based pharmacists via national pharmacy practice publications. The accredited programs will also be available for 2 years from that date on the publications' websites. There are subsequent publications planned to assure that pharmacists receive these critical education materials on a going forward basis via various pharmacy education publications/websites.

In addition to these continuing education materials, The Sponsor will provide pharmacies with patient education tools similar to the materials provided to physicians that allow for discussion between the pharmacist and patient on the appropriate use of modified-release opioid analgesics at the point of dispensing. (See Patient and Family Education Section below.)

3.2.1.7 "Practitioner's Guide to Prescribing Opioid Analgesics for Persistent Pain" Handbook

This practical clinical handbook was authored by Russell Portenoy, MD and Perry Fine, MD, two nationally-recognized experts on opioid analgesics and published by McGraw Hill. The handbook is intended to provide the essential information necessary for clinicians to responsibly prescribe opioid analgesics for persistent pain, including both clinical and risk management considerations. Development and dissemination of the handbook has been supported through an unrestricted educational grant from Endo; hard copies of the book have been distributed since mid-2004, and during 2005, an electronic version was posted to the nationally-renowned www.stoppain website.

3.2.1.8 "Advances in Cancer Pain: A Bedside Approach" Handbook

This handbook, authored by Ann Berger, RN, MD, Chief of Pain and Palliative Care Service at the National Institutes of Health (NIH), and published by The Oncology Group, is intended to provide practical, clinical information on the assessment and treatment of cancer pain. The handbook has been made available to both primary care clinicians and oncology specialists/nurses via an unrestricted educational grant from Endo. At least half of the handbook

focuses on the appropriate prescribing of opioid analgesics, including both clinical and risk management issues. The book has been available since 3Q 2004.

3.2.1.9 "Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain"

This handbook was prepared by a multidisciplinary committee of the APS to disseminate current information on effective therapy for acute pain and cancer pain to a broad audience of clinicians. Over 50% of the handbook focuses on the appropriate use of opioid analgesics including: dosing and compliance information; adverse effect recognition/treatment; and tolerance/addiction/ dependence issues. Endo makes this handbook available through its Scientific Affairs Department.

3.2.1.10 Risk Management Information/Tools for Clinicians

The Sponsor will provide clinicians with risk management information and risk management tools recommended by recognized experts in the fields of pain management and addiction medicine. Planned for inclusion are educational materials for patients and clinicians, a prototype patient/physician pain management agreement, and tools for assessing the patient's relative risk for misusing/abusing their medication.

3.2.1.11 AAPM/APS "Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain"

This joint consensus statement was prepared by the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) to provide guidance to clinicians on the under treatment of pain; to provide clarity on issues of addiction, diversion, tolerance, and side effects; and to promulgate principles of good medical practice with regards to the use of opioid analgesics for chronic pain. Endo has purchased quantities of the Consensus Statement which are made available through its Scientific Affairs Department.

3.2.2 Patient and Family Education

3.2.2.1 Patient and Family Brochure-"Understanding Your Pain: Taking Oral Opioid Analgesics"

This patient/family education brochure, supported by an unrestricted educational grant from Endo, was authored by Margo McCaffery, RN and Chris Pasero, RN, and edited by Russell Portenoy, MD. The brochure is intended to be provided to physicians and pharmacists for their patients being considered for or currently taking oral opioid analgesic therapy.

The brochure provides information to patients and family members on: opioid analgesics; their role in pain management; their potential side effects; information on addiction in patients taking opioids for the management of pain; and patient information on how to take their medication and track their pain. The booklet is available through the Endo sales force, the Scientific Affairs Department and the Endo corporate website, as well as at professional society meetings and educational conferences, including national pharmacist meetings such as the American Society of Health System Pharmacists, the Academy of Managed Care Pharmacy, and the American Society of Consultant Pharmacists. The brochure has been available in both print and electronic versions since 2Q 2004.

3.2.2.2 Pain Assessment Inventory and Patient/Family Education Materials

Since 2000, Endo has provided tear pads, which include the Brief Pain Inventory (BPI) and accompanying educational information on pain and pain assessment to physicians for their use in educating patients.

Upon publication of the national standards for pain assessment and management by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Endo supported the development of another patient/family education brochure entitled "Understanding Your Pain: Using a Pain Rating Scale." This brochure, developed through an unrestricted educational grant, was authored by Margo McCaffery, RN, Chris Pasero, RN, and edited by Russell Portenoy, MD. The brochure was endorsed by the JCAHO and has been distributed since 2001 in both print and electronic versions under the joint logo of JCAHO and Endo.

During 2004/2005, Endo developed and disseminated additional patient/family education pieces such as the aforementioned brochure on opioid analgesics, as well as materials, which stress the importance of compliance with opioid analgesic treatment regimens. Patient/family education pieces were also planned for 2006. Oxymorphone-specific materials will include any warnings and precautions from the Product Information with respect to appropriate dosing, potential side effects and their management, and the risks associated with modified-release opioids when they are inappropriately used by someone other than the patient for whom they were prescribed.

In addition, Endo will continue to support the development and distribution of patient/family education materials through national patient organizations such as the American Pain Foundation, the National Pain Foundation and the American Chronic Pain Association.

3.2.2.3 Pain Action

In March 2006 Inflexxion, with support from Endo and NIH, launched *PainAction.com*. This site is consumer-oriented and will provide patients and families with a variety of ways to become better informed about and better able to cope with their pain-related problems. It will also contain educational materials on the safe and appropriate use of opioids, self-assessment tools for patients to assess their relative risk of developing aberrant drug-related behaviors, proper storage and disposal information, and the importance of avoiding co-ingestion with alcohol and other specific drugs. Experts from the consumer side of pain management will consult on this project.

Consumers will also have the opportunity to utilize a variety of interactive tools (e.g., pain and symptom diaries) and self-report measures to be better able to consider how they can actively participate in their pain care. *PainAction* will be one of the most extensive consumer-oriented web programs focused on pain available on the Internet. In addition to Endo's educational grant support for the overall site, Inflexxion has received and will receive funding from NIH to further develop and test particular disorder-focused (e.g., back pain) components of *PainAction*. It is also likely that *PainAction* and *PainEdu* will be synergistic (i.e., pain clinicians will refer their patients to *PainAction* and consumers may recommend *PainEdu* to their clinicians).

3.2.3 Development of New Clinically Useful Validated Tools

3.2.3.1 Screener and Opiate Assessment for Patients with Pain (SOAPP)

Endo is currently supporting and will continue to support the development of what is referred to as the SOAPP tool – a prospective, patient self-report screening tool funded by grants from National Institute on Drug Abuse (NIDA), and developed by a team from Harvard University, Brigham and Women's Hospital, and Inflexxion, a healthcare research company with expertise in development of screening tools. With support from Endo, Inflexxion developed and rigorously tested Version 1 of SOAPP. At present they are expanding their SOAPP research with NIDA support to a much larger sample and making additional modifications on the scale that will be integrated into Version 2.

The SOAPP tool is a brief screening, self-report tool for those chronic pain patients being considered for opioid therapy. It will be easily completed and scored in less than 10 minutes in the waiting room of a physician's office or alternatively could be completed prior to the visit either as a brief paper questionnaire, online, or through an Interactive Voice Recognition (IVR) system. Such a tool could help classify patients along a continuum of greater or lesser likelihood of encountering misuse-related problems during a regimen of opioid medications. This information, along with interpretive cutoffs, would inform the healthcare provider that a given

patient may require extra monitoring while on pain medications or perhaps, that additional or alternative treatments should be considered.

Version 1 of SOAPP has already been the subject of a scientific publication as well as a number of professional society presentations. At present, the SOAPP Version 1 is being utilized by private physicians and in clinics as well as pharmacies; it is anticipated that this usage will increase significantly over the next year.

3.2.4 Sales Force Training

Endo fully understands the importance of responsible commercialization of this new extended-release opioid. An essential part of the approach will be to ensure our sales representatives are optimally prepared to provide physicians with the appropriate information supported by the approved label. Sales force training will be comprised of didactic and self-study modules as described below. Information regarding sales force compliance is also described below.

3.2.4.1 Therapeutic Class (Opioids and OPANA ER-specific) Training

Endo's sales force will undergo extensive training to assure that there is a clear understanding of the appropriate use of modified-release opioids, including the types of patients for which these medications are indicated, the physicians who treat these patients, and the laws and regulations that govern the use of CII controlled substances. Endo's sales representatives will also be trained on the appropriate use of OPANA ER, the use of educational tools developed for physicians, pharmacists, patients and caregivers, the adverse event profile of opioids as a class and the potential for abuse/misuse/diversion. The sales force will provide professional educational materials developed by the Sponsor to physicians and other healthcare professionals who request them. In addition to the therapeutic training listed below, the sales force receives training on adverse event reporting and risk management issues.

Therapeutic class training for the sales force includes: 1) the neuroanatomy of pain; 2) physiology of pain; 3) common etiologies of chronic and breakthrough pain; 4) pain assessment; and 5) pain management and the analgesic marketplace.

3.2.4.2 Appropriate and Responsible Selling of OPANA ER

Endo will conduct extensive training of its sales force, using a combination of self study/assessment tools and classroom training on the appropriate use of OPANA ER (the initial outline of this sales training program that was developed prior to product approval is provided in Appendix 1). Sales representatives will be required to demonstrate their understanding of the

approved prescribing information and the potential risks involved with improper use or abuse of OPANA ER through a written assessment prior to calling on physicians.

The objectives of the program are: 1) To familiarize Endo's sales and marketing staff with basic concepts of risk areas and risk management related to the promotion and sales of OPANA ER; 2) To ensure Endo's sales and marketing staff achieve a basic understanding of the laws governing relationships between pharmaceutical companies and their representatives and members of the provider communities; 3) To familiarize Endo's sales and marketing representatives with legal guidelines on pain management and the use of controlled substances to treat pain; 4) To provide Endo's sales and marketing representatives with specific examples of personal conduct that can create legal liability, including conduct related to off-label marketing of OPANA ER and improper relationships with providers and to familiarize Endo's sales and marketing representatives with additional legal liability issues relating to provider detailing, CME activities, and written marketing materials; 5) To insure a basic understanding of potential legal liability for providers who manage pain and use controlled substances to treat pain and to understand Endo's role in working with providers and patients to minimize the potential abuse and diversion of OPANA ER; and 6) To learn to show providers how to access and use the provider toolkit documentation and how to locate additional resources on these issues.

The sales force will play an important role in dissemination of educational tools, which aid in the appropriate use of OPANA ER. The Sponsor believes that this proactive approach will help those providers who prescribe OPANA ER to understand patterns and behaviors suggestive of patient opioid misuse, abuse, and diversion. The Sponsor's message in these interventions will be one of cultivating accountability regarding the proper use of OPANA ER.

3.2.4.3 Sales Force Compliance

The Sponsor intends to monitor the compliance of the sales force with approved marketing and sales guidelines in two ways. District sales managers, who will be thoroughly trained, will spend time in the field with each representative to assess the accurate delivery of appropriate messages and take corrective action with additional training, coaching, etc. to remedy the situation, if needed. The Sponsor will also utilize market research to monitor healthcare providers' comprehension and interpretation of promotional messages. If needed, the Sponsor can make adjustments to its sales training curriculum to diminish the likelihood of promotional message misinterpretation.

The Sponsor's sales representatives will have a responsible incentive/commission plan that is in line with industry standards. In order to qualify for the incentive compensation, each representative must be initially certified and annually re-certified on the education program. The

Sponsor's sales representatives will make sales calls on physicians who treat patients for whom a modified-release opioid is appropriate. The target audience includes pain specialists, oncologists, advanced practice oncology and pain management nurses, rheumatologists, physical medicine/rehabilitation specialists and primary care physicians who treat significant populations of moderate to severe chronic pain patients and are experienced prescribers of modified-release strong opioids.

The content outline for Endo's Pain Management and Oxymorphone Learning Systems is presented in Appendix 1. The intent of these programs is to create a sales force with extensive knowledge on the subjects of pain, pain treatments, healthcare providers who treat pain, benefits and risks of opioid pain medications and applicable laws, regulations and policies.

3.3 Tamper Resistant Prescription Pads

Prescription fraud, the alteration, forgery, or counterfeiting of a prescription, is a common means of diversion in the US. Endo will provide tamper-resistant prescription pads to prescribers, free of charge, to help protect healthcare professionals and patients from criminal drug diverters who attempt to illegally obtain controlled medications. These pads include several security features intended to help prescribers and pharmacists recognize and thwart common types of prescription fraud.

3.4 Oversight of the Distribution Chain

As for all of Endo's controlled substance products, the manufacturing and distribution chain is highly controlled and closely monitored. Endo employs sophisticated controls and monitoring at its manufacturing sites, in transit to Endo's distribution center, at the distribution center, and in transit to the wholesalers and large retail chains with appropriate CII vaults. All of Endo's manufacturing and distribution sites are rigorously inspected by the Drug Enforcement Agency (DEA) and all have close working relationships with their respective law enforcement agencies.

Endo's oversight includes physical and administrative controls as well as significant monitoring activities. Endo's physical and administrative controls at the manufacturers and distribution sites meet or exceed DEA requirements for CII materials. Endo's typical manufacturing and distribution chain controls are shown in Appendix 2; order management practices are presented in Appendix 3. Detection techniques, such as undercover security personnel and random checks, are employed in many cases. In addition, order management and transaction data are monitored frequently to look for unusual changes in deliveries to customers. For example, order and delivery discrepancies are tracked weekly and trends identified where discernable. These discrepancies may include events such as shortages, damage, and late deliveries. When trends

are observed, actions are taken which may include changes in commercial carriers, personnel, outer packaging, and delivery schedules. Additional monitoring of specific or anonymous complaints is performed through Endo's external website and customer service email address.

3.5 Postmarketing Surveillance

Endo's Pharmacovigilance and Risk Management Department will conduct proactive surveillance of OPANA ER adverse event reports received via post-marketing surveillance (spontaneous reports, scientific literature, post-marketing clinical investigations, and post-marketing epidemiological surveillance studies). Endo will review, investigate, process, and track adverse events for safety surveillance and safety signal detection. Reports of all serious adverse events to the FDA will be submitted in accordance with the current Federal Regulations. In addition, as per the FDA's request, the following post marketing reports will be submitted as 15 day alerts: any oxymorphone exposure in a child or adolescent (0-16 years of age) regardless of outcome and any medication error regardless of outcome. Endo will also submit the following reports as 15 day alerts: reports of misuse, abuse, addiction, dependence, or overdose, and reports of death or unexplained death.

3.5.1 Periodic Reports

Endo will assemble and submit periodic reports for all adverse events received for OPANA ER in accordance with current Federal Regulations. The periodic reports will be submitted on a quarterly basis for the first three years of marketing and yearly thereafter. These reports will be reviewed by Endo's Safety Review Board (ESRB) for trending and signal detection, specifically for increased reports of abuse, misuse or overdose.

In each of the quarterly Periodic Reports there will be a descriptive section relating to the risk management program and elements of the RiskMAP. As per the FDA's request, there will be summaries of the following: off label use and/or inappropriate prescribing, medication errors, pediatric exposures, and adverse events in opioid naïve patients. There will also be a review of the data obtained from secondary databases, post marketing research, and interventions (if undertaken).

3.5.2 Secondary Databases

Endo intends to monitor the following secondary surveillance databases on a quarterly frequency from product launch in line with the compilation of periodic safety reports: DAWN, TESS, FDA AERS, and RADARS. The data retrieved from the above mentioned secondary databases will be evaluated at the Endo Risk Management Team meeting and the Endo Safety Review Board

(ESRB) meeting. Summaries of any findings will be included within the Periodic Report in the Risk Management update report section.

3.5.2.1 National Addictions Vigilance Intervention & Prevention Program

Inflexxion is developing a national drug monitoring system for prescription and non-prescription drugs of abuse that will enable pharmaceutical companies, regulatory authorities and other customers to have immediate access to valid and reliable data about the abuse and misuse of specific medications throughout the US. This system, called the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), will provide companies with real-time product-specific medication data from an independent, scientifically-based third party. This will allow companies and regulatory agencies to identify abuse issues regarding particular products at an earlier point than what is available with current monitoring systems. NAVIPPRO will also examine comparative data and will be able to differentiate abuse and misuse of different brands and formulations. Among the unique, state-of-the-art features that are part of NAVIPPRO is the real-time reporting of product specific data as well as the application of statistical process control (SPC) methodologies to detect and localize signals of abuse and misuse. To our knowledge, NAVIPPRO will be one of the first systems to make SPC approaches a core analytical tool of a prescription drug risk management program.

The surveillance component of NAVIPPRO is being developed using an Internet version of Inflexxion's previously released CD-ROM based Addiction Severity Index – Multimedia Version (ASI-MV). The ASI-MV was researched and developed with National Institute of Drug Abuse (NIDA) support and is now being used at over 600 substance abuse treatment centers around the country. The Internet version of the ASI-MV, which will be a part of NAVIPPRO, is referred to as ASI-MV Online.net. The ASI-MV Online will expand upon the standard ASI-MV and will include questions and graphics designed to identify prescription drug problems and trends. Audio and video components of the Internet ASI-MV.net will be designed to assist respondents in accurately identifying prescription drugs used and in reporting their experience, including data such as specific illnesses, pain and medical treatment. In addition, questions will be added that seek to determine the sources of the medication taken by the respondent and pathways to abuse. To date, there have been about 250,000 administrations of the ASI-MV around the country. It is believed that using the ASI-MV Online as part of NAVIPPRO will increase the ASI-MV usage even further and provide Inflexxion and hence Endo and other companies with extensive, real-time product specific data and signal detection capability that is well beyond current data sources.

NAVIPPRO will help fulfill the vision of the FDA Advisory Committee in September, 2003, by providing detailed information for the first time on what proportion of patients entering

substance abuse treatment are patients with pain, whether they had addiction-related problems prior to therapeutic or non-therapeutic opioid exposure, what the sources are of diverted prescription opioids, and what are the risk factors for developing prescription opioid abuse.

3.5.2.2 Toxic Exposure Surveillance System (TESS)

Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of US poison centers. These data are used to identify hazards early, focus prevention education, guide clinical research, and direct training.

Endo will review the AAPCC annual report to identify OPANA ER exposures. Endo will then order abstracts for exposure and fatality cases associated with OPANA ER. The abstracts contain the following information: case number, patient's age, suspected substance(s), chronicity of the event, route of administration, reason for taking the suspected substance(s), and brief narrative surrounding the event. These reports will be analyzed, entered in the safety database, and reported to the Agency in accordance with Federal Regulations.

3.5.2.3 Researched Abuse, Diversion and Addition Related Surveillance (RADARS)

The Denver Health and Hospital Authority, in conjunction with the Rocky Mountain Poison Control Centers, operates the RADARS program. Forty poison control centers nationwide supply weekly data on abuse and misuse of prescription drugs. These data, which are de-identified, are collected and analyzed weekly as well as quarterly to identify any sentinel event or trends that may represent a signal. These data can be stratified down to a three digit zip code.

3.5.2.4 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related emergency department visits for the Nation and for selected metropolitan areas. DAWN also collects data on drug-related deaths investigated by medical examiners and coroners in selected metropolitan areas and States. The new DAWN implemented in 2003 now casts a wider net, and collects more details about each case. Please note that the new DAWN and its estimates for 2003 are not comparable to those for any prior years. DAWN is operated by the Substance Abuse and Mental Health Services Administration (SAMHSA), of the US Department of Health and Human Services.

DAWN provides semiannual estimates of the number of drug-related visits to hospital emergency departments based on a nationally representative sample (22 metropolitan areas) of

short-stay general hospitals located throughout the US. In 2003, 122 jurisdictions in 35 metropolitan areas and 6 states submitted mortality data to DAWN, which is published annually. Endo will monitor these DAWN reports, when released, to identify geographic trends which may not be identified through standard post-marketing surveillance. The Agency will be notified if any area of increased activity for OPANA ER is identified and Endo will initiate targeted education initiatives to the geographic region.

Endo has contracted with SAMHSA to access DAWN Live! data for the purpose of analysis and aggregate statistical reporting. This will allow Endo to have data that does not have a two year lag time. Please note that the above mentioned DAWN Live data have been de-identified; that is, these data do not contain direct patient identifiers or data items that could render a person identifiable. Also note that SAMHSA has denied access to comparator drug data from DAWN Live; information can be retrieved only for Endo marketed products or opioids in general. Since product approval and launch, Endo has supplied dosages, strength, and color information for both OPANA ER and OPANA to SAMHSA to be included in the tracking by DAWN. Endo will monitor DAWN Live on a quarterly basis, and the retrieved data will be used in the overall analysis of oxymorphone abuse and dependence.

3.5.2.5 FDA's Freedom of Information

Endo has a licensing agreement with DrugLogic to view safety data on all pharmaceutical products, which are received by DrugLogic from FDA under the Freedom of Information Act. DrugLogic provides information regarding the number of adverse events received for other marketed products. Adverse event information for OPANA ER that has been obtained via post marketing surveillance will be compared to other products of potential abuse, in this therapeutic class via FDA FOI data. Endo will use DrugLogic's Proportion Analysis Engine to look for deviations in reaction frequency for OPANA ER compared to an expected value derived from a background set of drugs (e.g., comparing Oxycodone ER and/or morphine).

DrugLogic's Proportional Analysis Engine looks for deviations in observed reaction frequency for a target drug or set of drugs as compared to an expected value derived from a background set of drugs (e.g., comparing a drug or drugs to all drugs, to specifically defined population set, or to drugs in a therapeutic category). The Proportional Reporting Rate (PRR), Chi-Square, and Confidence Level are calculated in each Proportional Analysis. On a quarterly basis, from product launch, Endo will run proportional analysis on oxymorphone in comparison to Oxycontin® tablets (Purdue Pharma L.P.), generic oxycodone ER (until December 2006 when generics will no longer be marketed) and/or all opioids (extended-release opioids for oxymorphone ER, immediate-release opioids for oxymorphone IR, or injectable opioids for oxymorphone injection). This analysis will identify occurrence of any adverse events for

oxymorphone that is either new or occurring in higher frequency than what is expected from the background (selected as comparator). A calculated PPR ≥2 with chi-square ≥4, N >2 could be considered as a signal of disproportionate reporting (potential signal devoid of clinical context) (Hauben *et al.*, 1995). Once a signal of disproportionate reporting is identified, the signal will be further investigated by searching for similar cases in the internal drug safety database from post marketing surveillance for additional review and evaluation.

3.5.2.6 Media Screening

In addition to reviewing the medical literature on a continual basis, Endo has subscribed a media screening service which reviews the lay press for articles pertaining to opioid abuse, with specific searches regarding OPANA ER. This search will be performed regularly with a report generated at least monthly. If areas of increased media coverage regarding abuse or diversion of the product are identified, further investigation will be undertaken.

Endo's media screening is performed monthly by CARMA International (www.carma.com), a global media analysis company, which has been contracted to review lay press articles for mentions pertaining to issues of opioids. Top tier newspapers in the nation and in certain geographic areas (identified by CARMA) that were previously identified as high-risk abuse areas for OxyContin (identified by the GAO; GAO 04-110 2003) were chosen as target areas to monitor. The search criteria is dynamic and the perimeters may be changed at anytime.

The search strategy identifies articles that contain any of the following key words: abuse, misuse, addiction, opioids, OPANA, oxymorphone, Percocet®, Oxycontin, DEA, law enforcement, painkiller, and oxycodone. Articles are reviewed that contain one of the search criteria and characterized by search term identified, geographic area, analgesic noted and then by newspaper in which the article appeared. The number of mentions is noted in each category. For example, Oxycontin may have 213 mentions noted for a month. These mentions are further stratified by law enforcement/criminal acts (123), abuse (66), corporate news (4) and narcotics (3). In addition, mentions are noted for each state. Massachusetts, New York and Pennsylvania have been noted in the last report to have the most mentions (3).

The review of monthly articles from CARMA, which provides number of mentions, will allow Endo to identify any areas that have a significantly increased number of mentions per month. Once a state or area is identified, the newspapers or media source can be utilized to further localize an area of interest. This can be further analyzed by reviewing the actual articles which are available. There are limitations to these searches, such as duplicate articles (from a syndicated press) appearing in numerous papers. Therefore, one article may appear in numerous

papers thus increasing the number of mentions. However, despite the limitations, these data may allow Endo to detect trends in certain areas.

3.5.2.7 Wolters Kluwer Data

Endo has recently changed vendors for prescription data surveillance from IMS to Wolters Kluwer. Wolters Kluwer Health's Phast Prescription audit measures the dispensing of prescriptions by retail pharmacies and mail order pharmacies on a monthly basis. Data are projected and includes approximately 80% of retail pharmacies and 46% of mail order pharmacy activity. Data can be aggregated from the state to national level as well specific geographic regions.

3.5.2.8 Primary and Secondary Prevention

Since a significant component of all prescription opioid abuse in this country is occurring in teens and young adults, working with Inflexxion, Endo will support two prevention programs designed to impact this population in a positive manner.

(1) *Mystudentbody: Drugs—MSB Drugs*. With NIH support, Inflexxion has developed and tested the country's largest and most extensive online suite of college health education programs, called *MyStudentBody (MSB)*. This suite of sites focuses on high risk areas for students such as Alcohol, STDs, Stress, Smoking, and Nutrition and so on. Endo's funding will allow Inflexxion to develop a new site to be called *MSB Drugs*. *MyStudentBody* is currently being used by about 80 colleges and universities with a total student population of nearly 500,000. Subscribers are increasing by about 35% per year. College administrators and health personnel have indicated to Inflexxion that they would welcome an *MSB* component focused on prescription drug abuse. They view this issue as the next most important college based problem after binge drinking. In many schools concerns about prescription medications even exceed concerns about marijuana. The *MSB: Drug* site will feature components like 'rate yourself,' peer stories, prevention strategies, tailored information and an online course. Because the *MSB* suite (without the prescription drug site) is already being used so extensively around the country, it is likely that the addition of this new area would further increase the number of schools and students who are using *MyStudentBody*. This would further the public health value of the program and teach students about problems associated with prescription opioid misuse. Other *MSB* sites have had major impacts on reducing high risk behaviors on campus and it is likely that *MSB Drugs* would have similar effectiveness.

(2) *Drugs4Real—D4R*. This online program is focused on preventing illicit and prescription drug abuse in high school students. *D4R* was developed and tested with NIDA support.

This program would be distributed to high schools around the country. It is highly interactive and was developed and tested with input from high school students. *D4R* would be another opportunity to reach out to a large, at risk population and prevent prescription opioid abuse. Inflexxion has worked extensively with the high school population and developed a number of other preventive programs that are used widely around the country.

3.5.2.9 Quantitative Internet Surveillance Program (QISP)

Many risk management programs include a program for monitoring the internet for mentions of specific prescription drugs in abuse-related contexts. Until recently none of these programs appeared to approach this issue in a systematic way. Endo has contracted with Inflexxion to support Inflexxion's Quantitative Internet Surveillance Program (QISP), which consists of routine monitoring of the rate of mentions of specific prescription opioid products on a group of selected abuse-related websites. Inflexxion has demonstrated that this innovative approach can track the mention rates and the rating of such mentions on Inflexxion's validated content rating system, and can distinguish mention rates of prescription opioids that are abused at different rates. The QISP will be used to monitor mentions of OPANA ER as well as other relevant comparators for any apparent trends in abuse of the product among prescription opioid abusers.

4. EVALUATION PLAN

4.1 Endo Safety Review Board (ESRB)

Endo has an established Safety Review Board (ESRB) to review adverse events and identify new safety signals and trends for all Endo products. The ESRB will review aggregate adverse event data received for OPANA ER on a quarterly basis at a minimum. However, if Endo identifies a trend or signal prior to the quarterly review, the ESRB will address these issues promptly and independently.

The ESRB consists solely of Endo employees since it is an integral component of our internal safety surveillance process. It is a multi-disciplinary team with representatives from Scientific Affairs, Medical Affairs, Clinical Research & Development (as needed basis), Regulatory Affairs, Project Management, Pharmacovigilance and Risk Management (chair), and Pre-clinical Drug Safety (as needed basis). The ESRB will review adverse event data of OPANA ER that have been collected as part of the post-marketing safety surveillance. As part of this surveillance, the ESRB will investigate and review all cases of clinical significance, misuse, abuse, dependence, overdose, death, and unexplained death to detect trends. Endo's review will

include patient demographics, physician demographics and information about the use of concomitant medications when available.

Various sources will be utilized to capture geographic data. These sources include post-marketing reporting, which may capture the city, state and zip code of the reporter; media surveillance, which captures the mentions geographic location; NAVIPPRO surveillance, which will capture geographic location of the subject; and prescription data from Wolters Kluwer (similar to IMS data), which may be stratified to a zip code level. TESS does not provide geographic information, nor does the DAWN database regarding ED mentions.

These data from the various sources noted above will be reviewed in conjunction with other available data such as post marketing reports and media reports in an attempt to identify trends that may represent areas of abuse. By utilizing various sources in aggregate there may be more power to detect trends.

In addition, information obtained will be compared to other products of potential abuse in this therapeutic class. Once Endo has analyzed the information, if a trend is identified, the Agency will be notified and targeted education and safety measures will be initiated in the geographic area identified.

4.2 Risk Management Team

In addition to ESRB, a Risk Management Team has been formed at Endo which will meet on a monthly basis to evaluate data collected from post-marketing surveillance, secondary databases, media screening, and Wolters Kluwer data in order to assess risks of OPANA ER while preserving its benefits. The team will be co-chaired by members of Pharmacovigilance and Risk Management Department and Regulatory Affairs with representations from Operations (supply chain), Clinical Development & Education, Market Research, Sales (as needed basis), Marketing department (as needed basis) and external consultants/advisors (as needed basis). The team will be responsible for evaluation of all reports of misuse, abuse, dependence, overdose, death, and unexplained death received for OPANA ER with the aim to identify trends and potential new safety signals. These reports will be used in conjunction with Wolters Kluwer data for geographic trending in regards to the above events. Risk assessment will include data that represent a numerator, including cases of spontaneous reports of abuse, misuse, and addiction. The denominator would estimate patient exposure by using Wolters Kluwer prescription data. Through these methods, a rough reporting rate can be calculated. In addition, to help identify trends, data will be further stratified by age, geographic region, and prescribing trends by specialty.

The team will be responsible for notifying the appropriate parties for intervention in the event a potential signal is identified. In addition, the Sponsor will send an analysis of all reports of misuse, abuse, dependence, overdose, death, and unexplained death received for OPANA ER on a semiannual basis to the Agency, and if a potential signal is identified, notify the agency at that time.

4.3 Risk Intervention

As per Endo's overall opioid RiskMAP, if Endo identifies any geographical areas of significant increases of abuse, misuse, or overdose with any of its opioids, including OPANA ER, Endo will take immediate and appropriate action, and notify the FDA, the specifics of which will depend upon the circumstances. Possible scenarios include:

- Diversion is suspected in distribution chain:
  - Endo will immediately alert the established security and management contacts at the manufacturing and distribution sites that may potentially be involved. These sites will investigate and search for possible diversion activities and will involve local DEA and law enforcement organizations as actionable details are discovered.
- Significant increase in cases of misuse, abuse, dependence, overdose, death, or unexplained death identified in specific geographic region by Risk Management Team:
  - Focused educational initiatives to targeted geographic area, which may be targeted towards health care providers, pharmacists, and/or the community
- Wolters Kluwer database identified high prescribing areas:
  - Refer to DEA for possible investigation unless internal investigation shows legitimate prescribing

4.4 Close Working relationships with Government Agencies and Officials

Endo has a history of working closely with the FDA and DEA on many issues that relate to its marketed products and will continue such a relationship with regards to OPANA ER. Endo will also work closely with other government agencies and officials wherever appropriate to minimize diversion, misuse, and abuse of OPANA ER.

4.5 RiskMAP Quarterly-Report

Endo will submit the quarterly periodic reports for OPANA ER and per the FDA include a section on RiskMAP progress.

5. CONCLUSION

Endo Pharmaceuticals Inc. is a pharmaceutical company focused on improving the care of pain for patients through the development of alternative analgesics. OPANA ER has been found to be effective in the treatment of moderate-to-severe chronic pain and will offer an alternative to patients. Endo understands the potential risks inherent in OPANA ER and thus has developed a RiskMAP that can effectively minimize the known risks of abuse, misuse and diversion of OPANA ER while preserving its benefits.

6. REFERENCES

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APPENDIX 1 – PAIN MANAGEMENT LEARNING SYSTEM

MODULE 1: ANATOMY AND PHYSIOLOGY OF THE NERVOUS SYSTEM

I. The Neuroanatomy of Pain
   A. The Neuron
   B. The Peripheral Nervous System
   C. The Central Nervous System

II. Pain
   A. Physiology of Pain
   B. Subjective nature of Pain
   C. Pain Characteristics

III. Common Sources of Chronic and Breakthrough Pain
   A. Low Back Pain
   B. Osteoarthritis
   C. Cancer Pain
   D. Breakthrough Pain
   E. Other Sources of Pain

IV. Pain Assessment
   A. History and Physical
   B. Key Questions in Assessing Pain
   C. Rating Scales

MODULE 2: NEUROPATHIC PAIN (*NOT INCLUDED AS PART OF OPANA/OPANA ER SALES TRAINING*)

MODULE 3: PAIN MANAGEMENT AND THE ANALGESIC MARKETPLACE

I. Is Pain a Significant Health Problem?
   A. Morbidity and Health Care Costs
   B. The Patients' View
   C. The Health Care Professionals' View
   D. Role of Pharmaceuticals in Pain Management

II. Analgesic Product Classes

A. Non-opioid Analgesics
B. Opioid Analgesics
C. Guidelines for Using and Switching Opioids
D. Opioids as Controlled Substances

III. Routes of Administration
A. Oral
B. Intramuscular & Intravenous
C. Transdermal
D. Transmucosal (oral, rectal)
E. Spinal and Epidural

OPANA/OPANA ER LEARNING SYSTEM

MODULE 1: PRODUCT INFORMATION FOR OPANA ER

I. Overview of OPANA Extended-Release
A. TimeRx® Extended Release System
B. Pharmacology of OPANA Extended-Release
C. Prescribing Concerns

II. Clinical Studies
A. Phase I
1. PK
2. Special Populations
3. Drug/drug interactions
B. Phase III Studies
1. Osteoarthritis
2. Low Back Pain
3. Cancer Pain
4. Extension Studies (2-year data for safety)
C. Studies in Progress (Phase III/IIIB)

III. Annotated Package Insert
A. Annotated Package Insert Text

MODULE 2: PRODUCT INFORMATION FOR OPANA

I. Overview of OPANA

A. Pharmacology of OPANA
B. Prescribing Concerns

II. Clinical Studies
A. Pharmacokinetic
B. Post surgical pain

III. Annotated Package Insert
A. Annotated Package Insert Text

MODULE 3: PROMOTING OPANA ER IN THE ANALGESIC MARKETPLACE

I. Appropriate Messages for OPANA ER
A. Selling Messages for OPANA ER
1. Efficacy
2. Safety/Tolerability
3. Formulations and Pharmacokinetic Profile
4. Dosing
5. Appropriate Patients
B. Selling Messages for OPANA
1. Efficacy
2. Safety/Tolerability
3. Appropriate Patients

II. Key Competitors
A. Long-acting Morphine Products
1. Characteristics
2. Available Products
3. Advantages and Disadvantages
4. Key Selling Messages
B. Long-acting Oxycodone
1. Characteristics
2. Advantages and Disadvantages
3. Key Selling Message
C. Fentanyl Patch Products
1. Characteristics
2. Advantages and Disadvantages
3. Key Selling Message
D. Short-acting Morphine Products
1. Characteristics
2. Available Products
3. Advantages and Disadvantages

4. Key Selling Messages

E. Short-acting Oxycodone Products
   1. Characteristics
   2. Available Products
   3. Advantages and Disadvantages
   4. Key Selling Messages

F. Actiq
   1. Characteristics
   2. Advantages and Disadvantages
   3. Key Selling Messages

III. Target Health Care Professionals Who Prescribe/Dispense/Oversee Use of Strong Opioids

A. Physicians
   1. Oncologists
   2. Anesthesiologists
   3. Neurologists
   4. Pain specialists
   5. Rheumatologists
   6. Physical Medicine/Rehab
   7. PCPs who treat moderate to severe chronic pain

B. Nurses/Nurse Practitioners/PAs

C. Pharmacists

D. Pain Specialty Clinics

E. Managed Care Medical and Pharmacy Directors

IV. Anticipated Physician Questions and Concerns

A. Anticipated Issues for OPANA ER
   1. Efficacy
   2. Safety
   3. Reimbursement/Availability

B. Anticipated Issues for OPANA
   1. Efficacy
   2. Safety
   3. Reimbursement/Availability

MODULE 4 APPROPRIATE AND RESPONSIBLE SELLING OF OPANA ER

I. Introduction

A. Training Objective: Endo's Risk Management Sales Training program is designed to provide guidance to the Endo sales force to *stay safe* and *on course* when selling OPANA ER.

B. Learning Objectives

Learning Objective #1 – Familiarize Endo's sales and marketing staff with basic concepts of risk areas and risk management related to the promotion and sales of OPANA ER. Explain Endo's risk management plan and its basic components, including post-marketing surveillance and adverse event reporting.

Learning Objective #2 – Achieve a basic understanding of the laws governing relationships between pharmaceutical companies and their representatives and members of the provider communities.

Learning Objective #3 – Familiarize Endo's sales and marketing representatives with legal guidelines on pain management and the use of controlled substances to treat pain. Also, achieve a basic understanding of legal guidelines supported by professional organizations.

Learning Objective #4 – Provide Endo's sales and marketing representatives with specific examples of personal conduct that can create legal liability, including conduct related to off-label marketing of OPANA ER and improper relationships with providers. Familiarize Endo's sales and marketing representatives with additional legal liability issues relating provider detailing, CME activities, and written marketing materials.

Learning Objective #5 – Insure a basic understanding of potential legal liability for providers who manage pain and use controlled substances to treat pain. Understand Endo's role in working with providers and patients to minimize the potential abuse and diversion of OPANA ER.

Learning Objective #6 – Learn to show providers how to access and use the provider toolkit documentation and how to locate additional resources on these issues.

II. Introduction and Overview of Endo's Risk Management Plan
- A. Why do I need training on the legal issues and risk management?
  1. Endo's Corporate Role in Handling Legal Issues and Basic Risk Management Concepts
     a. Endo Code of Conduct
     b. Endo Policies for Sales Representatives
  2. DEA and FDA roles in Risk Management
  3. Endo's role in minimizing potential for abuse and diversion of OPANA ER.
  4. The individual sales and marketing representatives' role in minimizing potential for abuse and diversion of OPANA ER.

III. Survey of Applicable Federal and State Regulatory and Legal Materials and Guidelines from Professional Organizations

A. What regulatory and legal materials relate to my role as an Endo sales or marketing representative? How do these materials apply to my promotion of OPANA ER?
1. DEA Regulations and Statutes
   a. 21 CFR and applicable sections. Focus will be on prescribing issues.
   b. 21 USC and applicable sections. Focus will be on prescribing issues and the illegal distribution of controlled substances.
2. FDA Regulations
   a. Importance of the Label
   b. OPANA ER Label
   c. Safety Warnings
   d. Introduction to Off-Label Issues
3. Department of Veterans Affairs – Guidelines on the Use of Controlled Substances to Treat Chronic Pain
4. Department of Justice (DOJ) Health Care Fraud and Kickback Statutes. Overview of Safe Harbor Issues.
   a. Overview of DOJ's investigative and prosecution efforts impacting pharmaceutical companies and their representatives including examples
5. Department of Health and Human Services-Office of Inspector General (HHS-OIG) Compliance Guidelines
   a. What are they?
   b. Do they apply to sales and marketing representatives?
   c. Learning to sell and market within the guidelines.
6. State Controlled Substances Acts
   a. What are they?
   b. How do they differ from the Federal Controlled Substances Act?

c. Who enforces state controlled substances acts when it comes to prescription drugs?

7. Guidelines and Position Statements of Professional Organizations
   a. American Medical Association
   b. American Pain Society
   c. American Academy of Pain Medicine
   d. American Academy of Pain Management
   e. American Society of Interventional Pain Physicians
   f. National Guideline Clearinghouse
   g. International Society for the Study of Pain
   h. World Health Organization

V. Specific Risk Areas and Risk Management Efforts

A. What kind of actions put Endo and its individual employees at risk? What role does the sales and marketing rep play in risk management?

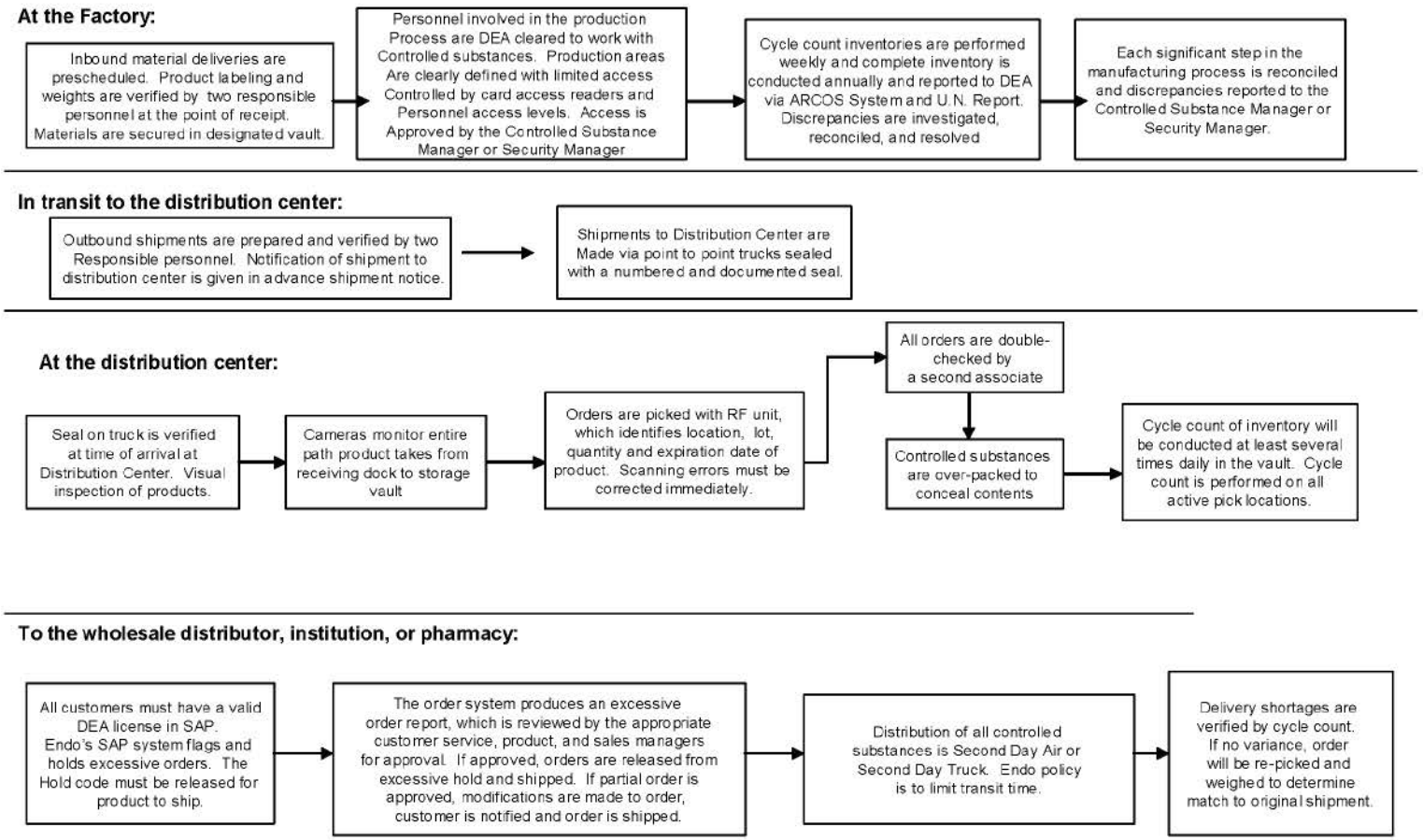
1. Risk Areas in the Sales and Marketing of OPANA ER
   a. Endo's relationship with the FDA
   b. Endo's relationship with Providers
   c. Endo's relationship with Pharmacists and Pharmacy Benefits Management (PBMs)
   d. Endo's relationship with Managed Care Organizations (MCOs) and Other Health Care Benefit Programs
   e. Endo's relationship with the Consumer
   f. Endo's relationship with Competitors

VI. Description and Distribution of the Healthcare Professional Risk Management Toolkit

A. Overview of Provider Toolkit
   1. Provider Assessment/Inventory
   2. Provider/Patient Treatment Agreement
   3. Pain Assessment Tool
   4. Patient/Caregiver Brochure
   5. Tamper-proof prescription pads

B. Distribution of the Provider Toolkit

APPENDIX 2 – ENDO SAFEGUARD TO PREVENT OPIOID DIVERSION



APPENDIX 3 – ORDER PROCESSING AND DISTRIBUTION

Excessive Orders Management

Endo Pharmaceuticals SAP Order Management System flags and holds all excessive orders for all Endo products (controlled substances II, III and ambient products). The order remains on hold and does not ship until the hold code on the order is released.

Specifically, orders are put on excessive hold when:

- The order exceeds the past 3 months average shipped quantity, and/or
- The order exceeds the past 12 month's average shipped quantity.

The system produces a report that provides customer information to Customer Service. The Customer Service Representative (CSR) has a guideline of orders that they are allowed to release which is documented in the UPS SCS Endo Work Instructions. For any order that is above this quantity, Customer Service will send the order information to the Manager, Customer Service and Distribution. The Manager, Customer Service and Distribution will review the following:

- Customer's Inventory Levels – if applicable
- Customer's Ordering history for the past 6 months to review recent trends in ordering pattern

If the Manager, Customer Service and Distribution are unable to release the order based on the information above, she will request the CSR to call the customer and ask why they have placed a large order. If the customer provides an adequate answer, the Manager, Customer Service and Distribution will provide approval to the CSR to release the order. Some examples of adequate answers are:

- Customer has acquired a new customer or new contract
- Sales have increased
- Customers have consolidated warehouses

Following the customer order quantity inquiry, if the Manager, Customer Service and Distribution are still unable to release the order, she will forward all of the information to the following people for approval:

- Product Manager
- Vice President, Marketing
- Senior Vice President, Commercial Business
- Senior Vice President, Operations

Approval to release the order must be provided by a Vice President or Senior Vice President. If approved those orders are then released from excessive hold and shipped. If partial quantities are

approved, Customer Service modifies the order, notifies the customer and then the order is shipped. If the entire order is rejected, Customer Service also notifies the customers. All of this information is documented in the notes of the order.

New Product Launch Orders

The excessive order program impacts initial launch orders for a new product since there is no order history in SAP. Many initial launch orders are put on hold as excessive. All launch orders are released from excessive hold until a history is built in SAP. The CSR is in constant communication with the Manger, Customer Service and Distribution on order quantities and the Manager, Customer Service and Distribution approves all launch orders. Information of the initial launch orders is documented in the notes section of the order

Receipt Process

All inbound product shipments are received into Quarantine Hold.

Endo Pharmaceuticals will notify the warehouse with an advance shipment notification for all shipments prior to arrival. Information will include product code, lot number, quantity, Manufacturer, and Purchase order number.

Upon arrival of the truck in the distribution center, receivers will verify that all seals are intact and match the freight bill prior to opening the doors.

The receiving associates will visually inspect all inbound products before and during the off loading process. If any discrepancies are found (i.e., damages, shortages, overages) the receiving associate will contact the operations supervisor and the QA representative on site.

All inbound CII product will be off loaded to the secured vault area immediately upon arrival. Cameras will monitor the path the product follows from the receiving dock to the storage vault.

Product will be physically counted. Once the count is complete the product will be physically bagged with an orange quarantine bag and a quarantine placard will be applied to each pallet.

The actual quantities, lot number and expiration dates are posted via the RF unit.

Picking Process

All CII orders are picked with a RF unit. This RF unit will identify the location, lot, quantity and expiration date of the product that needs to be picked. Each bar code is scanned with the RF to identify the product that needs to be picked. If the wrong product is scanned an error or a warning message will appear on the RF unit. The error must be corrected before moving on to the next line of the order.

Any discrepancies (location, product, lot expiration or quantity) are bought to the supervisor's attention immediately for resolution.

All orders are double checked by another warehouse associate. The orders are checked for ensure the correct product, lot number, and quantity is picked.

The packing list for each order will include instructions to notify Customer Service within 48 hours for any discrepancies.

Product Packing

All controlled substances are enclosed in a secondary corrugate container before they are shipped. Specifically, there is no way to know what is in the primary container, because it is over packed to secure it. Full pallets of controlled substance are enclosed with a corrugate pallet cover and then the entire pallet is wrapped with black wrap.

Distribution

Distribution of all of Endo's controlled substances and ambient products will be by second day air and/or 2nd day truck. Endo will continue its policy to limit the amount of time that all products, especially the controlled substances, are in transit.

Cycle count of inventory is conducted daily in the vault prior to any orders shipping. A cycle count is performed on all active picking locations after a batch of orders (each batch is approximately 40-50 orders).

After a batch of orders is completed, a warehouse associate will generate a report that indicates all locations that need to be counted. A warehouse associate will go to each location and count the number of units in the location. After the count is completed the count sheet is provided to the team lead or supervisor. The team lead or supervisor will run another report that will indicate the number of units that should be in each location. If the count does not match, the supervisor

will count the locations again. If the count still does not match, the warehouse will begin opening all the packages until they can find the mistake.

No orders are shipped until the inventory is reconciled.

Reported Shortages

Currently, customers call Customer Service with complaints regarding shortages or overages. Customer Service tracks, via an Error Log, all Customer Service errors (shortages, overages, damages, mis-shipments etc). If the error is a short ship, that is less is received then shipped, or an over ship, that is more is received then ordered, Customer Service and Distribution immediately begin to analyze the situation to determine cause and path forward.

A shortage or overage reported by a customer will be verified in the following manner:

(1) Customer Service will verify if an opposite complaint has been received, that is, if a shortage is reported, Customer Service checks the Error Log to see if an overage of the same amount of the product in question has been reported which would account for the shortage.
(2) If the opposite complaint had not been received, an inventory cycle count will be conducted on the product in question to determine whether a variance exists; that is, does physical inventory match system inventory.
(3) If no variance is found, the order will be re-picked and re-weighed to check if the weight supports the original weight of the shipments